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Titel des Beitrags: Glucocerebrosidase deficiency and mitochondrial impairment in experimental Parkinson disease.

Abstract: Gaucher disease is an autosomal recessive disease, caused by a lack or functional deficiency of the lysosomal enzyme, glucocerebrosidase (GCase). Recently, mutations in the glucocerebrosidase gene (GBA) have been associated with Parkinson’s disease (PD) and GBA mutations are now considered the most important genetic vulnerability factor for PD. In this study, we have investigated (i) in vivo whether inhibition of the enzyme glucosylceramide synthase by miglustat may protect C57Bl/6 mice against subchronic 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication and (ii) in vitro whether a decrease of GCase activity may render dopaminergic neurons susceptible to MPP(+) (1-methyl-4-phenylpyridinium) or alpha-synuclein (?-Syn) toxicity and amenable to miglustat treatment. We could demonstrate that reduction of glucocerebroside by inhibition of glucosylceramide synthase partially protects mice against MPTP-induced toxicity. Conversely, we could show that inhibition of GCase activity with conduritol-B-epoxide (CBE) enhances both ?-Syn and MPP(+) induced toxicity in vitro. However, only CBE-induced enhancement of MPP(+) toxicity could be reversed by miglustat. Moreover, we were unable to reveal any alterations of complex I
activity or cell respiration upon treatment with either CBE or miglustat. Our findings suggest that the reduction of GCase activity rather than an accumulation of glucocerebroside increases aSyn toxicity.